4-[^{18}F]Fluoro-L-*m*-tyrosine

4-[^{18}F]FMT

The MICAD Research Team

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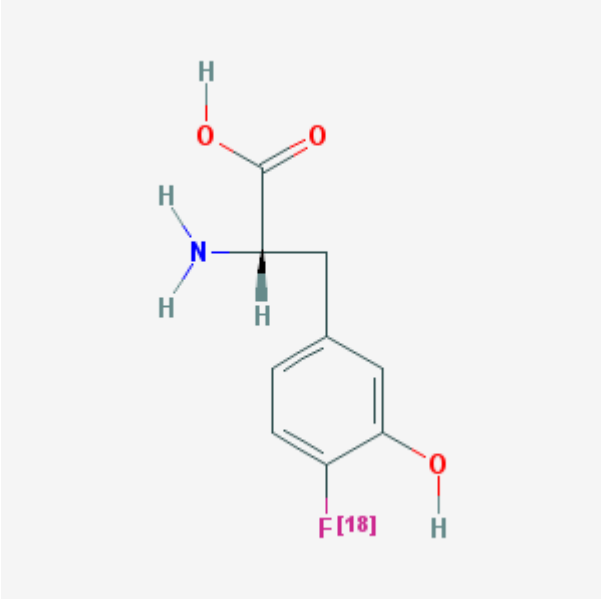
Chemical name:	4-[^{18}F]Fluoro-L-*m*-tyrosine
Abbreviated name:	4-[^{18}F]FMT
Synonym:	4-FMT, 4-[^{18}F]Fluoro-3-hydroxy-L-phenylalanine
Agent Category:	Compound
Target:	Aromatic L–amino acid decarboxylase (AAAD)
Target Category:	Enzyme-substrate
Method of detection:	Positron Emission Tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents • Non-human primates



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Background

[PubMed]

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4-[^{18}F]Fluoro-L-*m*-tyrosine (4-[^{18}F]FMT) is a noncatecholic radioligand developed for positron emission tomography (PET) imaging of dopaminergic metabolism and function in the central nervous system (CNS) (1, 2). It is an analog of dihydroxyphenylalanine (L-DOPA) labeled with ^{18}F, a positron emitter with a physical $t_{½}$ of 109.7 min.

Dopamine is an important neurotransmitter that regulates and controls human movement, motivation, and cognition (3). It is also associated with human behaviors such as reward, reinforcement, and addiction. There are four main dopaminergic pathways in the CNS (4). Two pathways that originate in the ventral tegmental area project toward the cortex and the limbic area, a third pathway projects from the hypothalamus toward the pituitary gland, and a fourth pathway projects from the substantia nigra to the striatum. Neurons located in these pathways release dopamine as a neurotransmitter at their terminals. There are five known dopamine receptor subtypes, which are categorized as D_1-like or D_2-like (5). The D_1-like receptor subtypes (D_1 and D_5) couple with the Gs protein to activate adenylyl cyclase, and the D_2-like subtypes (D_2, D_3, and D_4) couple with G proteins to inhibit adenylate cyclase. Abnormal changes in the dopaminergic system can lead to pathologic conditions such as Parkinson's disease, schizophrenia, Huntington's disease, depression, Gilles de la Tourette syndrome, narcolepsy and other neuropsychiatric disorders (6).

Radiotracer imaging with specific radiolabeled molecular probes can measure pre-, post-, and intrasynaptic aspects of the dopaminergic system (6). [^{18}F]Fluoro-L-dopa ([^{18}F]FDOPA), which was developed by Firnau et al. (7), was the first presynaptic probe to be developed. It was also the first molecular probe used by Garnett et al. (8) to visualize human brain dopamine *in vivo*. Like endogenous L-DOPA, [^{18}F]FDOPA is converted by the enzyme aromatic L-amino acid decarboxylase (AAAD) to the dopamine analog fluorodopamine. Thus, PET imaging of [^{18}F]FDOPA allows *in vivo* visualization and assessment of dopamine function in the brain. However, the use of [^{18}F]FDOPA is complicated by the peripheral metabolism of this agent. DeJesus et al. (9) proposed the synthesis and use of [^{18}F]FMT and other tyrosine analogs as possible alternative dopamine probes because they lack the enediol moiety required of catecholamine-*O*-methyltransferase (COMT) substrates. Both *o*- and *m*-tyrosines are excellent substrates for AAAD but *m*-tyrosine is a normal constituent in the brain (10). Three isomers of [^{18}F]FMT, 2-, 4-, and 6-[^{18}F]FMT, were initially produced and studied (11) Both 4-[^{18}F]FMT and 6-[^{18}F]FMT appeared promising as early studies showed that they provided good image contrast (1, 12, 13).

Synthesis

[PubMed]

DeJesus et al. (9, 11) reported the synthesis of [^{18}F]FMT *via* direct electrophilic fluorination of D,L-*m*-tyrosine with acetyl[^{18}F]hypofluorite ([^{18}F]AcOF). [^{18}F]F_2 was produced from [^{18}O]O_2 by a two-bombardment method. The final labeled product was purified by high-performance liquid chromatography (HPLC). HPLC analysis showed

that approximately 80% of the D,L-*m*-tyrosine had reacted, and ^{19}F-NMR analysis indicated that the final product was a mixture of 2-, 4-, and 6-[^{18}F]FMT isomers in the proportion of ≈36:11:52, respectively. The radiochemical yield was 71 ± 5% (n = 3; decay correction based on [^{18}F]AcOF activity) after purification. The specific activity was 3.7–7.4 GBq/mmol (100–200 mCi)/mmol).

Perlumtter et al. (14) prepared 4-[^{18}F]FMT by using regioselective fluorodemercuration of a 4-mercurio precursor with ^{18}F-labeled acetylhypofluorite. The mucurio precursor was synthesized in a three-step sequence from 3-hydroxy-L-phenylalanine. 3-hydroxy-L-phenylalanine ethyl ester was obtained by refluxing 3-hydroxy-L-phenylalanine in absolute ethanol saturated with dry hydrogen chloride for 5 h. This ethyl ester compound was reacted with di-*t*-butyl dicarbonate at room temperature under argon for 24 h to give *N*-(*t*-butoxycarbonyl)-3-hydroxy-L-phenylalanine ethyl ester. The resulting compound was then reacted with mercuric trifluoroacetate at room temperature for 5 days. The bulky *t*-butoxycarbonyl *N*-protecting group facilitated the specific precipitation of the mercurio precursor from the reaction mixture. Radiosynthesis was carried out by bubbling ^{18}F-labeled acetylhypofluorite into a solution of the mercurio precursor at room temperature for 10 min. The solvent was evaporated, and the residue was hydrolyzed with 55% hydrogen iodide. The radiochemical yield was 25% (corrected for decay) with a synthesis time of ~60 min. The chemical, radiochemical, and enantiomeric purities were >99%, and the specific activity was ~74 GBq/mmol (2 Ci/mmol) at the end of the synthesis.

Namavari et al. (15) described the synthesis of 4-[^{18}F]FMT based on a regioselective radiofluorodestannylation procedure. In this method, *N*-(trifluoroacetyl)-3-acetoxy-4-(trimethylstannyl)-L-phenylalanine ethyl ester was first synthesized as a precursor. The radiosynthesis was carried out by electrophilic fluorodestannylation of the precursor and exhaustive deprotection of the acid, amine, and phenol. Briefly, ^{18}F-labeled fluorine was bubbled into a solution of the trimethyltin derivative in Freon-11 at room temperature for 15 min. After purification by chromatography, the radiolabeled intermediate was hydrolyzed with 48% hydrogen bromide at 130°C for 10 min. The reaction mixture was partially neutralized with 3-N sodium hydroxide and then purified by HPLC. More than 99% of the 4-[^{18}F]FMT was chemically and radiochemically pure. Chiral HPLC determined the enantiomeric purity to be >99% and the total tin determined by inductively coupled plasma spectrometry was <15 parts per billion. The total synthesis time was 60 min, and the radiochemical yield was 11% at the end of bombardment.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

DeJesus et al. (2) used rat striatal synaptosomes to evaluate whether 4-[^{18}F]FMT was a good dopa decarboxylase substrate. For 4-[^{18}F]FMT, the Michaelis constant (K_m) was determined to be 54 μM and V_{max} was 450 pmol/min per g. In comparison, 6-[^{18}F]FMT had K_m = 53 μM and V_{max} = 390 pmol/min per g.

Animal Studies

Rodents

[PubMed]

Melega et al. (1) conducted central and peripheral metabolism studies of 4-[^{18}F]FMT in rats. 4-[^{18}F]FMT was injected as an i.v. dose of 51.8 MBq/kg (1.4 mCi/kg) in rats pretreated with 5 mg/kg s.c. carbidopa, an AAAD inhibitor. Specific brain radioactivity localization (striatum/cerebellum ratio = 1.7 n = 4) was observed at 30 min. HPLC analysis showed that 66 ± 5% of the striatal radioactivity was associated with 4-fluoro-3-hydroxyphenylacetic acid (FPAC), 19 ± 3% was 4-fluoro-3-hydroxyphenylethylamine (FMA), 5 ± 1% was *O*-sulfoconjugate (FMA-sulfate), and only 9 ± 4% was 4-[^{18}F]FMT. The formation of FPAC was mediated by central monoamine oxidase (MAO) oxidation, and the formation of FMA was mediated by AAAD decarboxylation. In the plasma, 67 ± 11% of the radioactivity at 30 min was 4-[^{18}F]FMT , 27 ± 7% was FMA sulfate, and 7± 2% was FPAC. The plasma level of 4-[^{18}F]FMT was 60% at 120 min.

In direct comparisons between 4-[^{18}F]FMT, 6-[^{18}F]FMT and [^{18}F]FDOPA, Barrio et al. (12) conducted regional brain distribution and peripheral metabolism studies of these radioligands in rats. Each rat received 51.8 MBq/kg (1.4 mCi/kg) of radioactivity by i.v. administration and carbidopa s.c. 60 min before the radioligand injection. The distribution of striatal metabolites of 4-[^{18}F]FMT appeared to be different from that of FDOPA or 6-[^{18}F]FMT. At 30 min after injection, 66 ± 5% of the 4-[^{18}F]FMT radioactivity had converted to 4-FPAC whereas the predominant metabolite of 6-[^{18}F]FMT and [^{18}F]FDOPA was 6-FMA. In peripheral metabolism, both 4-[^{18}F]FMT and 6-[^{18}F]FMT produced measurable amounts of decarboxylation metabolites even with carbidopa pretreatment. The authors related this finding to the AAAD activity that is higher in rat serum (60.0 pmol/min per ml) than in human serum (≈1 pmol/mn per ml) (16).

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

PET studies of 4-[^{18}F]FMT were conducted in monkeys (n = 3) with doses of 185-370 MBq (5–10 mCi) and specific activity of 37–74 GBq/mmol (1–2 Ci/mmol) (1). Three monkeys were pretreated with 5 mg/kg i.v. carbidopa 60 min before 4-[^{18}F]FMT injection. PET imaging showed rapid radioactivity accumulation in striatal structures and rapid clearance from the cerebellum. The striatum/cerebellum radioactivity ratio increased to ≈4 at 3 h. Little radioactivity was observed in the bone structures. Chemical

analysis of arterial plasma showed that 4-[^{18}F]FMT remained the predominant species and decreased to 60% of the total radioactivity at 120 min. FMA-sulfate slowly increased to ≈35% at 120 min and FPAC remained at <6%.

Barrio et al. (12) studied the *in vivo* kinetic and biochemical behaviors of 4-[^{18}F]FMT in three monkeys. Each monkey received ≈37 MBq/kg (1 mCi/kg) i.v. 4-[^{18}F]FMT after 1 h pretreatment with 5 mg/kg carbidopa. PET imaging at 90–120 min after injection showed that the radioactivity accumulation pattern was consistent with localization of central dopamine-rich structures, but also showed accumulated in AAAD-rich innervation sites. The striatum/cerebellum ratios were 2.76 ± 0.20, 3.48 ± 0.40, and 4.57 ± 1.16 at 60 min, 90 min, and 120 min, respectively. In comparison, [^{18}F]FDOPA had ratios of 1.47 ± 0.15, 1.85 ± 0.17, and 2.06 ± 0.09, respectively. Peripherally, no COMT-mediated products were produced, but products of AAAD-mediated decarboxylation were found. The AAAD activity in monkey serum was 44.7 pmol/min per ml (16). The AAAD-mediated decarboxylation produced 4-FMA which was then converted to FPAC by MAO oxidation or conjugated by phenolsulfotransferase. In comparison, 6-FMA produced from 6-[^{18}F]FMT was not subject to the same peripheral MAO oxidation.

Hayase et al. (17) reported that PET imaging of 4-[^{18}F]FMT in monkeys showed specific accumulation in AAAD-rich areas of the striatum, which reached a striatum/cerebellum ratio of 3 at 2 h. In a study with four monkeys rendered hemi-Parkinsonian by unilateral intracarotid artery infusion of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), Hayase et al. (18) used 4-[^{18}F]FMT imaging to show a reduction in AAAD activity in the MPTP-lesioned striatum. The mean lesioned-striatum/cerebellum ratio was 1.3 compared with 3.9 in the normal contralateral region.

Human Studies

[PubMed]

No publication is currently available.

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